

PRELIMINARY AMENDMENT

Please amend the above-identified application as follows:

IN THE CLAIMS

Please amend Claim 1 as follows.

1. (twice amended) A method for the treatment of established joint inflammation in a human or non-human patient in need thereof comprising administering to the patient an effective anti-inflammatory amount of a C5 blocker, wherein the C5 blocker does not block the functions of early complement components and does not interfere with cellular immune responses seen after immunizing mice with bovine type II collagen.

REMARKSI. Introduction

This amendment to claim 1 was originally submitted response to the final Office Action mailed October 2, 1996 in 08/311,489, from which the present application claims priority. Applicants request that the Commissioner charge \$195.00 and any other fees required by this paper to Deposit Account. With the extension, this response is due on March 3, 1997. Should any extension of time be required, the Commissioner is requested to consider this a petition therefor. The Commissioner is hereby authorized to charge

any fees required by this paper to deposit account No. 01-0483.

Claim 1 is hereby being amended in order to limit the scope of the pending claims (all the rest of which depend from Claim 1) to only those C5 blockers that do not interfere with cellular immune responses seen after immunizing mice with bovine type II collagen. Support for this change can be found, e.g., in Example 3 of applicants' specification. See particularly the paragraph spanning pages 50-51. Also see Figure 6 and the description thereof in the first full paragraph of page 23.

## II. The §103 Rejections

The Examiner had rejected claims 1-14 in 08/311,489, and again in the present application, under 35 U.S.C. §103 in the as allegedly being obvious over the combination of the teachings of Sindelar et al (U.S. Patent Application No. 5,173,499; the "'499 patent") in view of Auda et al. (Rheumatol. Int., 1990); Wurznier et al. (Complement Inflamm.); and Montz et al. (Cell. Immunol.).

**Previous arguments:** In their amendment of June 14, 1996 in 08/311,489, Applicants argued that the art cited by the Examiner would not have given one skilled in the art a reasonable expectation of success in treating inflammatory joint disease. The Examiner had interpreted this argument

as indicating that applicants were arguing that the Sindelar patent is not enabled. Applicants respectfully reassert these arguments as they apply to the then pending rejections in the belief that they do not bear upon whether or not the '499 patent is enabled.

The '499 patent claims certain compounds and a method of use for those compounds in "treating a patient with an immune disorder or a disorder involving undesirable or inappropriate complement activity." In their amendment of June 14, 1996 in 08/311,489, applicants raised the question of whether a worker of ordinary skill in the art would have had a reasonable expectation of success in treating inflammatory joint disease with the compounds of the '499 patent.

The treatment of inflammatory joint disease is not specifically claimed in the '499 patent. The enablement provision of §112 only requires that

there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility.

In re Vaack 20 USPQ2d 1438, 1445 (CAFC, 1991)  
(footnote omitted)

Thus, applicants' assertion that a worker of ordinary skill in the art would not have had a reasonable expectation of success in treating inflammatory joint disease with the compounds of the '499 patent did not indicate that applicants were asserting that the claims of the '499 patent were not enabled (nor, for that matter, that they were).

**The current amendment:** Applicants have hereby amended pending Claim 1 (from which all of the other pending claims depend) to require that the claimed C5 blocker does not interfere with cellular immune responses seen after immunizing mice with bovine type II collagen. This change distinguishes applicants' invention from the invention of the '499 patent and in particular from the uses for the C5 inhibitory compounds discussed therein in that such compounds inhibit both complement activity and cellular immune responses.

Sindelar et al. point out in the "Summary of the Invention" of the '499 patent that "[t]he compounds of the present invention also exhibit immunosuppressive activities, such as, for example, the ability to inhibit natural killer activity, lymphocyte proliferation, and T cell activation." ('499 patent column 8, lines 15-18.) They go on to point out that "[t]he compounds of the present invention can inhibit immune activity. In particular, the compounds of

the invention inhibit cell-mediated immune function." ('499 patent column 22, lines 45-47.) The relative potencies of the C5 inhibitory compounds discussed in the '499 patent with regard to the inhibition of complement activities and cellular immune responses can be gauged from, *inter alia*, the data set forth in their Figures 2-7 and Tables VI-X.

Figure 2 of the '499 patent demonstrates that a 50% inhibition of C5a production was not obtained at concentrations below 6 mM. Also note that, in contrast to the Examiner's assertion in 08/311,489 that "the blockers of the '499 patent also do not appear to substantially interfere with the cleavage of C3," (office action of October 2, 1996 in 08/311,489, page 3, lines 5-7) Figure 2 shows that, within the range of blocker concentrations tested, C3a production was inhibited by more than 80%.

Figures 4-7 of the '499 patent set forth the results of experiments analyzing cellular immune responses. In contrast to the millimolar concentrations required to achieve 50% or greater inhibition of C5a production, each of the four aspects of the cellular immune response tested was inhibited by more than 50% at sub-millimolar concentrations of the test compound. See also Tables VIII, IX, and X, which summarize results obtained with several related compounds.

Applicants respectfully submit that the above review of

the data of the '499 patent demonstrates that, while the compounds of the '499 patent may inhibit complement component C5, any such inhibition is concomitant with inhibition (blocking) of the functions of early complement components, and with substantial interference with cellular immune responses. Applicants believe that workers of ordinary skill in the art would understand that any reasonable expectation of success for any of the various therapeutic uses discussed for such compounds would be based upon the presence of both the complement inhibitory and cellular immune response inhibitory properties of such compounds. This belief is supported by the content of the DECLARATION OF YI WANG PURSUANT TO 37 C.F.R. § 1.132 submitted in 08/311,489 on September 12, 1996, a copy of which is submitted herewith, which applicants respectfully request be reconsidered in light of the above amendment and discussion.

In view of the above considerations, applicants respectfully traverse the prior rejections in 08/311,489 on the grounds that the teachings of Sindelar et al. do not make any of applicants' claims as hereby amended obvious, and that the combination with the Auda et al., Wurznier et al., and Montz et al. references does not make up for this deficiency. Applicants thus submit that the present

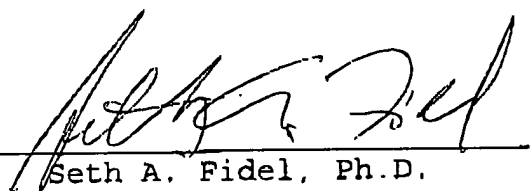
invention is not obvious, and earnestly request that the Examiner reconsider and withdraw the prior rejections under §103 in 08/311,489.

### III. Conclusion

In view of the foregoing, applicants respectfully submit that the present application is now in condition for allowance. Accordingly, entry of this amendment, consideration of the amended claims, and the issuance of a notice of allowance for this application are respectfully requested.

Respectfully submitted,

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